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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,578	09/10/2003	Zsuzsanna Nagy	43962-010810	4669

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,578	NAGY, ZSUZSANNA	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/18/05;12/8/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *7,9-16 and 19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8, 17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 1-6, 8, 17 and 18 in the reply filed on 12/8/2006 is acknowledged. The linking claims in the restriction requirement dated 9/19/2006 were inadvertently identified as claims 1-3 and 5. The correct linking claims were 1-6, 17, and 18. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 7, 9-16, and 19-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/8/2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8 , 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection has been changed from a scope of enablement rejection to an enablement rejection, and thus is considered a new ground of rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art and State of the art. The art concerning diagnosis of Alzheimer's disease (AD) by assaying for a cell cycle defect at the G1/S transition is unpredictable. In a paper published five years after applicant's priority date, Nagy (Nagy, Z, Biochim. et Biophys. Acta, 2006) teaches that diagnosis of "definite" Alzheimer's can only be made by histopathological assessment after autopsy, and that clinical diagnostic criteria (NINCDS-ARDRA) have a very high false negative rate (see page 1, ¶ linking first and second columns). The instant specification teaches much the same (page 1, line 16 -page 2). Nagy et al (Neuro. Lett., 2002, of record), using methods that appear to be the same as described in the instant specification, teach differences in the relative lengthening of the G1 phase upon rapamycin treatment of lymphocytes from control patients and from those already diagnosed using the NINCDS criteria (see page 82, second column, last ¶ to page 83, second column, and Fig. 1). The lymphocytes from all patients diagnosed with some form of dementia (i.e. the preAD (pre-clinical AD), AD (probable AD), ADM (AD and other types of dementia), possAD (possible AD), and DNOS (dementia other than AD) groups) were found to be less responsive to rapamycin than the control cells in the G1 lengthening assay (Fig. 1A). This is significant because: 1) these results are different than those presented in the instant application (e.g.

compare Fig. 1A of Nagy et al with Fig. 2 of the instant application, in particular the possAD and DNOS groups relative to the control, and the AD and ADM groups relative to each other); and, 2) without prior diagnosis of the patients using the NINCDS criteria, as taught by Nagy et al, there could be no diagnosis of AD, such prior diagnosis not being a limitation of the instantly claimed methods. Regarding 1) above, this discrepancy calls into question the reliability and predictability of the instantly claimed methods. Regarding 2) above, in Fig. 1A of Nagy et al, the DNOS group is less responsive to rapamycin than the control. According to the instantly claimed methods, this would lead to a misdiagnosis of these patients as having AD, which is clearly not correct. The same would be true if the G1/S diagnostic assay for AD was performed as described in Figs. 3 and 5 of the instant specification, in which the DNOS group represented the most resistance to rapamycin or H_2O_2 treatment in the age-corrected graphs. These same experiments, as reported by Nagy et al (Figs. 1B and 1D), appear to use data without age-correction, which is questionable in the diagnosis of AD (see the previous Office Action, page 5). Nevertheless, the rapamycin effect on patient cells was concluded to have no significant difference from controls, and the H_2O_2 effect did not differentiate between the controls and the preAD patients.

Furthermore, the instantly claimed methods and specification ignore the fact that merely assaying for a defect in the G1/S checkpoint, or relative resistance to the effects of a G1 inhibitor such as rapamycin, then diagnosing patients with such a G1/S defect as having AD would misdiagnose many cancer patients as having AD. Chan (Brit. J. Canc., 2004) and Wendel et al (Nature, 2004) document cancer cells resistant to rapamycin. Absent evidence to the contrary,

testing these rapamycin-resistant cells using the instantly claimed methods would produce results similar to those seen for the AD cells, i.e. a resistance to the effects of rapamycin.

Given the above, the state of the art regarding the diagnosis of AD only by assaying for a G1/S checkpoint defect is poorly developed. The development of such an assay would have to be done empirically.

Number of working examples. Applicants have provided no working examples of diagnosing AD by merely performing a G1/S checkpoint assay as instantly claimed. The disclosed working examples require a prior diagnosis of patients using the NINCDS criteria, and a comparison of the groups diagnosed by such criteria in a G1 phase lengthening assay.

Amount of guidance. Applicants provide no direction or guidance for diagnosing AD as instantly claimed (e.g. see claim 1). The specification requires the skilled artisan to practice trial and error experimentation to develop a reliable and effective assay that differentiates AD from other dementias and cancer by merely assaying for a G1/S checkpoint defect.

Scope of the invention. The claims are broad in nature and read on diagnosing AD by merely assaying for a G1/S checkpoint defect in any non-neuronal cell, which could be a reduction in effectiveness of the checkpoint (i.e. as in claim 2), or an increase in the effectiveness of the checkpoint (within the scope of claim 1). There is no description or guidance for such an assay for an increase in the effectiveness of the G1/S checkpoint, let alone an association of such an increase with AD. Claim 3 reads on testing the responsiveness of the cells of the claimed methods to any cell division inhibitor (apparently an inhibitor of any phase of the cell cycle, not necessarily the G1/S checkpoint), and extrapolating a resistance to such an inhibitor, relative to control cells, to the diagnosis of AD. However, the instant specification indicates that a G2

inhibitor did not distinguish between AD and DNOS patients (doxorubicine, Fig. 4). Claim 5 reads on inducing cell cycle arrest (apparently in any phase of the cell cycle, not necessarily the G1/S checkpoint) in the cells of the claimed methods, and extrapolating a resistance to such arrest, relative to control cells, to the diagnosis of AD. However, such cell cycle arrest did not distinguish between AD and DNOS patients (H_2O_2, Fig. 4), and some of the cell cycle arrest stimuli recited in claim 6 do not arrest cells in G1, but rather G2 (i.e. ionizing and UV radiation).

Nature of the invention. The invention involves the unpredictable art of diagnosing AD.

Level of skill in the art. While the level of skill in the art of assaying for cell cycle defects is high, the level of skill in the art of diagnosing AD by assaying for such defects is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by amendment of the claim.**

Claim 8 recites the limitation "stimulus that induces cell cycle arrest " in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Any rejection not repeated in this Office Action is withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER